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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Seed Intellectual Property Law Group PLLC
701 Fifth Avenue, Suite 5400
Seatle, WA 98104

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,409	LEDBETTER ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2009*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *435,436,438,439,446 and 447* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *435,436,438,439,446 and 447* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/29/09* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 435, 436, 438, 439, 446 and 447 are all the pending claims for this application.

2. Claims 414-434, 437 and 440-445 were cancelled, Claims 435, 436, 438 and 439 were amended and new Claims 446 and 447 were added in the Response of 7/13/09.

3. Claims 435, 436, 438, 439, 446 and 447 are all the pending claims under examination.

4. This Office Action contains new grounds for rejection. This Office Action is final.

Information Disclosure Statement

5 The IDS of 10/29/09 has been considered and entered. The initialed and signed copies of the 1449 forms are attached.

6. If the examiner has inadvertently overlooked an IDS in the application file, applicant is kindly requested to alert the examiner to this oversight in the response to this Office action.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Written Description

7. The rejection of Claims 414-416, 418, 420, 422-426, 428-431, 437 and 439 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

Applicants comments on p. 5 of the Response of 7/13/09, and the amendment to delete the rejected claims overcomes the rejection.

Enablement

8. The rejection of Claims 414-416, 418, 420, 422-426, 428-431, 437 and 439 are rejected under 35 U.S.C. 112, first paragraph, because the specification *does not reasonably provide enablement* for fusion proteins comprising for element (i) of Claim 414: a single variable domain, or variable domains comprising any substitution at any one or more positions 9, 10, 11, 12, 108, 110 or 112 in the VH domain; and for element (ii) of Claim 414 any altered wild type hinge; and for any fusion protein having 99% identity to the fusion protein of SEQ ID NO:166 or 246 (Claim 437) is withdrawn.

Applicants comments on p. 5 of the Response of 7/13/09, and the amendment to delete the rejected claims overcomes the rejection.

Claim Rejections - 35 USC § 103

9. The rejection of Claims 414, 415, 420, 422, 423, and 425-429 under 35 U.S.C. 103(a) as being obvious over Schilling (US 20050084933; published April 21, 2005; filed December 18, 2003; cited in the PTO 892 form of 2/20/09) in view of Ledbetter et al.

(USPN 6623940; published September 23, 2003; cited in the PTO 892 form of 2/20/09) is withdrawn.

Applicants comments on p. 6 of the Response of 7/13/09, and the amendment to delete the rejected claims overcomes the rejection.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 435, 436, 438, 439, 446 and 447 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (WO 88/04936; published 7/14/88; cited in the IDS of 10/29/09) in view of Welschof et al. (Human Immunol. 60:282-290 (1999); cited in the IDS of 10/29/09) and Schilling (US 20050084933; published April 21, 2005; filed December 18, 2003; cited in the PTO 892 form of 2/20/09).

Claims 435, 436, 438, 439, 446 and 447 are interpreted as being drawn to a fusion protein comprising a chimeric 2H7 antibody comprising the VH and VL domains linked by a linker (scfv) and being fused to a mutant human IgG1 hinge and further being fused to wild type human gamma 1 domain, where the mutant hinge comprises , and the protein binds CD20 (Claims 435 and 436, respectively) or a composition comprising the fusion proteins (Claims 439 and 446, respectively), or a fusion protein comprising the VH and VL domains of 2H7 scFv Ig (parent antibody; SEQ ID NO: 689) linked by a linker (i.e., scfv) and being fused to a human IgG1 hinge comprising (CSC-S) and further being fused to wild type human gamma 1 domain, and the protein binds CD20 (Claim 438), or a composition comprising the fusion protein (Claim 447).

Despite the examiner's best efforts at piecing together the structure of the fusion protein of Claim 438, the examiner still can not identify which of the full length sequences for the numerous constructs depicted throughout the specification and the Sequence Listing, would correspond to the claimed fusion protein. Applicants are kindly requested to simplify their claim drafting for purposes of advancing prosecution and to expedite sequence searching.

It would have been prima facie obvious to have produced the 2H7 scfv- hinge-WTCH2-WTCH3 fusion proteins based on Robinson and Welschof.

Robinson discloses a chimeric mouse 2H7 antibody where the mouse Ig constant domains are replaced with the human gamma 1 constant domains including the human hinge, CH1, CH2 and CH3 domain. Robinson discloses the human constant domains confer strong ADCC and ACC activities while retaining antigen specificity of

the fusion protein for CD20. Robinson does not disclose the 2H7 antibody in the form of a scfv or where the hinge portion of the constant region is a mutation of any of the above hinges.

Welschof discloses scfv antibodies and human IgG1 hinge regions where the hinge region of IgG1 comprises 3 parts, namely, the upper, middle and lower subregion. The rigid middle hinge is the part between the two SS-bridges, also known as the core hinge subregion. Hinge peptides are shown in Table 1 and comprising the “E-variant” and the "Q-variant” where the core peptide domain is (C-P-P-C). Welschof discloses that mutations in the hinge help to prevent auto-antibody responses to a recombinant antibody administered in vivo where the auto-antibody recognizes epitopes in the hinge domain. Thus according to Welschof it is a balance to include residues for proper folding just as it is important to remove epitopes that are antigenic.

Schilling teaches generating fusion proteins [0157], using the CTLA4Ig protein as a working embodiment comprising the extracellular domain of CTLA4 joined to an Ig moiety comprising all or a portion of an immunoglobulin molecule, or a portion of an immunoglobulin constant region such as all or a portion of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD or IgE which include the hinge, CH2 and CH3, and mutated forms of the constant region [0195; 0212]. Schilling teaches:

“The Ig moiety can have one or more mutations therein, (e.g., in the CH2 domain to reduce effector functions such as CDC or ADCC) where the mutation modulates the capability of the Ig to bind its ligand by increasing or decreasing the capability of the Ig to bind to Fc receptors. For example, mutations in the Ig moiety can include changes in any or all of its cysteine residues within the hinge domain. For example, as shown in FIG. 8, the cysteines at positions +130, +136, and +139 are substituted with serine.

The Ig moiety can also include the proline at position +148 substituted with a serine, as shown in FIG. 8" [0212].

The difference between the prior art of Schilling and the claimed fusion protein is that the fusion protein of Schilling does not expressly include an scfv as the binding domain and having the linker sequence of Gly-Gly-Gly-Ser and binding CD20 on a tumor cells.

The ordinary artisan would have been motivated and been assured of success in having produced the instant claimed fusion proteins based on Robinson and Welschof. Each of the references appreciates the non-specific immune response generated against a foreign antibody which occurs through residues in the constant regions and also the hinge region. Robinson teaches preserving the antigen binding integrity, making a chimeric antibody and using the full intact human IgG1 constant domain retains the ADCC and ACC properties and to modify the antibody further insofar as reducing non-specific immunity, Welschof discloses creating scfv molecules, and further suggests that the huam IgG1 hinge is s further source of non-specific immunity because of antigenic epitopes found in the hinge. Thus to create a CD20 binding fusion protein that had all the advantages of CD20 binding specificity, reducing non-specific immunity to itself and having potent ADCC and.or ACC properties, the ordinary artisan would have considered the advantages of the elements taught individually in both Robinson and Welschof and with a reasonable expectation of success based on their reduction to practice for each reference.

At the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Schilling and Ledbetter to use the fusion protein of

Schilling comprising any altered hinge domain and comprising a substituted proline falling within the transition region between the altered hinge and the truncated constant region of the fusion protein for producing the CD20-binding fusion protein of Ledbetter where the heavy and light chain variable domains were present in the construct with the linker sequence and the fusion protein having the ability to bind CD20 on tumors. One would have been motivated to do this because of the advantages of producing a fusion protein according to Inouye, and the advantages of including both the heavy and light chain variable domains in a scfv as noted by Ledbetter. One would have had a reasonable expectation of success to modify the fusion protein of Schilling to increase the repertoire of fusion proteins according to Ledbetter to produce a CD20 binding fusion protein because of the results of Schilling and Ledbetter.

MPEP 2142 states in part: " Exemplary rationales that may support a conclusion of obviousness include:…(E) “Obvious to try”- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;…” and “the rationale to support a conclusion that the claim would have been obvious is that “a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.”KSR, 550 U.S. at ___, 82 USPQ2d at 1397.” It is the examiner’s position that it would have been obvious to try the combinations of linker domains and hinge domains where the VH and VL domains were essentially similar to the parent 2H7 anti-CD20 antibody, because

they were limited in number and where both art references provided direction as to which possible choices were likely to be successful.

Secondly, in order to combine all of the various elements and to screen them for binding would not require any more guidance than presented in the art references. Applicants have not shown how the references teach away from recombinant techniques for generating chimeric proteins and screening the resultant protein.

Finally, it is not a requirement that the Examiner establish that the cited art contains all the elements of the rejected claim, as the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR, 550 U.S. at 418.

Conclusion

11. No claims are allowed.

12. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 10/29/09 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/

Primary Examiner, Art Unit 1643